

Maintenance Treatment in Recurrent Depression: Current and Future Directions The First William Sargent Lecture

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The legacy of Will Sargent

When William Sargent died in 1988 at the age of 81, he had made his mark on British psychiatry. He had exerted considerable influence on US psychiatry as well. This was especially obvious during a time when physical treatments were hardly the fashion in US psychiatry. As *The Times* (1988) stated at the time of his death, he had made psychiatry more respectable by keeping it close to the medical model. He did a great deal to make depression intelligible to general practitioners and, therefore, to make it a legitimate, respectable illness.

Almost 25 years ago, Dr Sargent was asked to give the Watson-Smith lecture at the Royal College of Physicians. For this lecture, later published in the *British Medical Journal* (Sargent, 1966), he chose as his subject psychiatric teaching in the general teaching hospital. His primary goal in this lecture was to re-establish the clinical unity of psychiatry and general medicine through examples of the treatment possibilities beginning to open up in both general medicine and psychiatry, which he hoped could be pursued jointly. Included in this broad discussion was the treatment of depression. Dr Sargent stressed that treatment for depression could now be conducted for much shorter periods than previously. He described the experience that he and his colleagues had had since the late 1950s in prescribing antidepressant drugs. He finished this lecture on a fairly optimistic note. "Now with all physical treatments combined if necessary, practically all cases of depression in good previous personalities can be helped, and recurrences often prevented or greatly modified. Chronicity should by now become a very rare occurrence indeed." That may have been the case in the UK, but, unfortunately, it was not yet the case in the US.

It is interesting to note that this lecture at the Royal College of Physicians was considered sufficiently important for a commentary on it to be published in *The Times* six months later (1966). The commentary, entitled "Psychotherapy in Its Widest Sense", concluded that current clinical research in medicine and psychiatry was now becoming impressive. It made three major points:

- (a) with all the exciting work now going on with pharmacotherapy, we might begin to understand more about the underlying pathophysiology of mental disorders
- (b) medications should not be considered the end-all or be-all of our armamentarium
- (c) the mentally and emotionally afflicted can be restored to a useful and satisfying role in society only if the term 'psychotherapy' is used in the widest possible sense to include all the tools now available to physicians, family doctors, and clergymen alike, each performing their particular art to aid the mentally disturbed.

Twenty-five years later, our emphasis will be on maintenance or preventive treatment, rather than on a review of the treatment of depression in general. I would argue that until very recently too much of our attention was devoted to the treatment of acute depression and much less attention was given to what is really the critical issue - prevention of future episodes (National Institute of Mental Health (NIMH), 1985). William Sargent would have agreed that recurrent mood disorders are clinically significant phenomena. They represent major public health problems associated with a considerable risk of suicide, diminution of lifetime productivity by anywhere from 25 to 50%, and some risk with each new episode that the disorder will become chronic.

Strategies for the treatment of depression

What is the best way to think about an overall treatment strategy for depression? Perhaps the most important thing we can teach our colleagues, our patients, and their families is the early recognition of the disorder, coupled with early initiation of treatment of the acute episode. The second important concept is what many people have termed 'continuation treatment', which is aimed at reducing the likelihood of relapse, the return of symptoms before the episode has run its course. The third aspect of a complete

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treatment strategy is prophylaxis, aimed at preventing new episodes of illness.

Early recognition of depressive episodes

What new information do we have about the importance of early recognition? We now have empirical data suggesting that the earlier we intervene, the shorter the episode will be (Kupfer *et al*, 1989). In a study that we completed 2 years ago, we treated a group of 45 patients with recurrent depression who, on average, had been depressed about 4 months before they entered treatment. We defined stabilisation as 3 weeks of a Hamilton Depression Rating Scale score of ≤ 7 , and once treatment with a combination of imipramine (mean = 218 mg/day) and interpersonal psychotherapy (IPT) (Klerman *et al*, 1984), was initiated it took approximately 9 weeks to stabilise these 45 patients. Following a period of 17 additional weeks of continuation treatment with the combination of imipramine and IPT, they entered a randomised maintenance treatment trial. These particular subjects were among those assigned to treatments in which active medication was discontinued. Each of these 45 patients had a recurrence of major depression within 1–2 years of discontinuing medication. Following their recurrence, they were treated exactly as we had treated them for the episode that had originally brought them to our attention. The difference was that instead of initiating treatment after they had been depressed an average of 16 weeks, in each case we were able to initiate treatment after they had been depressed less than 4 weeks, because they were under our continuous observation. The length of time required to stabilise these patients was moderately but not significantly shorter the second time; however, since treatment was initiated much earlier in the course of the episode, the length of time that the average patient spent in depression was shortened from 6 months to less than 3 months. These results strongly suggest that we should try to achieve a collaborative arrangement with our patients and their families to inform us of new symptoms as quickly as possible so that treatment can be initiated early in the course of the episode and suffering minimised.

Continuation treatment

With respect to continuation treatment, it is important to reiterate what has been advocated by clinicians on numerous occasions, namely that the phase of continuation treatment should last a minimum of 4–6 months after the acute symptoms have resolved. A number of studies (Prien & Kupfer, 1986; Kupfer

& Frank, 1987; Frank *et al*, 1990a) point to the fact that earlier discontinuation or even reduction of dose significantly increases risk of relapse. In their review, Prien & Kupfer (1986) examined how long continuation drug treatment of depressive episodes should be maintained to ensure that the episode is over. On the basis of the six extant placebo-controlled investigations of continuation drug therapy in depression, it seems that the relapse rate over a 2–8-month period of observation on placebo was 50%, and that the relapse rate on active drugs which consisted in most cases of a tricyclic antidepressant, was 22%. Using the National Institute of Mental Health–Psychopharmacology Research Branch (NIMH–PRB) collaborative study on long-term psychopharmacological treatment (Prien *et al*, 1984), they concluded that the patient should be free of significant symptoms for 16–20 weeks before treatment is discontinued. Secondly, before one decides that a 'syndromal declaration' represents a new episode, a minimal interval of 16–20 weeks without significant psychopathology is necessary. Finally, the authors emphasised the need to focus on mild, as well as moderate and severe, symptoms, since even mild symptoms, in patients who usually do not function at that level, might represent an indication that the episode had not run its course.

The recently completed Pittsburgh study by Frank *et al* (1990b) offers another opportunity to examine issues relating to continuation treatment and the rate of relapse during continuation treatment. In this study on combination maintenance treatment (imipramine and IPT), open treatment was conducted during the acute and continuation phases prior to the double-blind, randomised maintenance trial. Of the 157 patients who entered the continuation phase, 128 completed the 17 weeks of this treatment phase. Data from the Pittsburgh studies show that the addition of psychotherapy, as well as a family educational workshop, may reduce the rate of relapse to below 10%. The overall relapse rate of 7.6% observed in the Pittsburgh sample during continuation treatment is considered low for this patient population and certainly merits replication (Kupfer & Frank, 1987; Frank *et al*, 1990a). It also appears that combined continuation treatment has an advantage in terms of keeping patients engaged in treatment. In fact, 7% of subjects dropped out or needed to be withdrawn for non-compliance (Frank *et al*, 1990a). When the data on drop-out and non-adherence rates in this study were compared with those of the NIMH–PRB study, it appeared that the design of the present study had affected treatment adherence in a positive way (Frank *et al*, 1985). Two features of the design which may be responsible for

this difference are the addition of psychotherapy to the treatment regimen and a strong emphasis on educating both patients and their families regarding the nature of the illness and the nature of the treatments being used.

Maintenance treatment

Now let us turn to the topic of primary emphasis: prophylaxis or maintenance treatment. There have been a relatively small number of studies of true maintenance treatment of recurrent unipolar disorder. One of the major studies (Glen *et al*, 1984) was conducted in the UK and, together with a collaborative study conducted in the US (Prien *et al*, 1984), has had a major impact on treatment strategies for long-term prophylaxis. Yet, in both of these investigations results were less than satisfactory. Even those patients in the active treatment conditions generally had less than a 50% probability of remaining well for 2-3 years. It should be noted that in both of these investigations, upon entry into the maintenance phase of the study, patients assigned to the active medication conditions were reduced to approximately half the dose of medication used to resolve the acute episode.

In 1982 we began a new long-term treatment trial at the University of Pittsburgh (Frank *et al*, 1990b). We attempted to answer several questions in this investigation which had been highlighted in a NIMH-sponsored Consensus Conference on Recurrent Disorders. First, we wanted to know what would happen if we did not decrease the acute treatment dose but continued the full treatment dose in maintenance? Would we achieve a higher level of treatment efficacy than had previously been reported? A second question was what would happen if we were to combine a maintenance form of a depression-specific psychotherapy, such as IPT, with maintenance pharmacotherapy. This idea was actually very much in keeping with Dr Sargent's notions of 25 years ago. Our study design (Fig. 1) consisted of five maintenance conditions: maintenance interpersonal psychotherapy (IPT-M) alone; IPT-M with placebo; IPT-M with active imipramine; medication clinic visits with placebo; and medication clinic visits with active imipramine. After randomisation, these fully stable patients were followed monthly for 3 years or until they experienced a new episode of illness. It was felt that this design would allow us to answer the two questions raised above as well as a number of others.

The first thing that we noted was that those patients who received medication clinic visits and placebo did rather poorly (Fig. 2), but no more

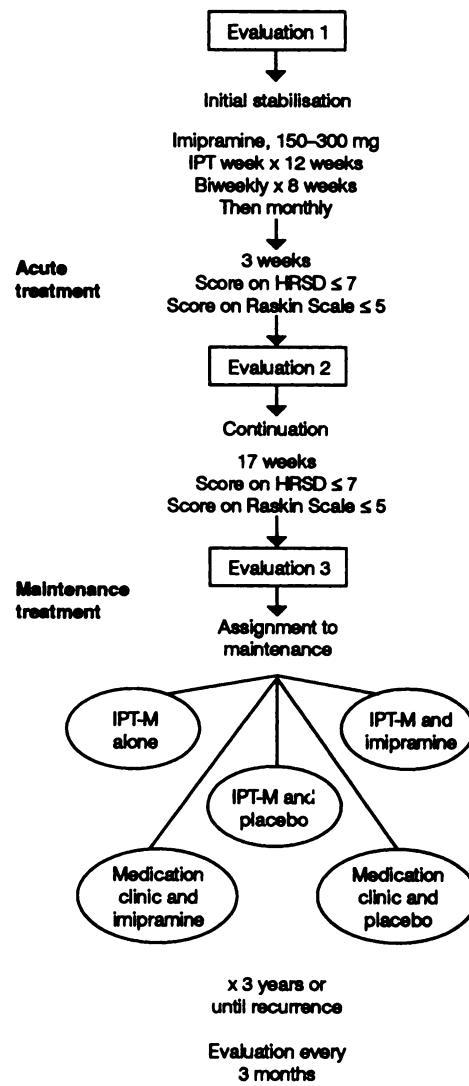


Fig. 1 Maintenance therapies in recurrent depression study.

poorly than in the study reported previously by Prien *et al* (1984), and, in fact, our observations were very consistent with the Glen *et al* (1984) report, as well as with other studies which have shown that fewer than 20% of recurrently depressed patients survive 2 years without a new episode in the absence of some treatment intervention. For patients treated with active imipramine (average dose: 208 mg/d) either with or without psychotherapy, the cumulative probability of survival was over 80% ($P < 0.0001$) Frank *et al*, 1990b). As noted above, previous studies showed that survival rates with active medication

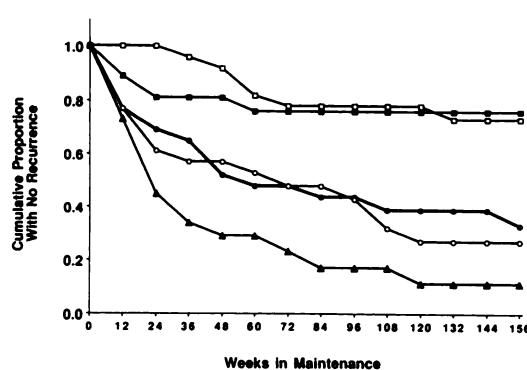


Fig. 2 Outcome of the maintenance therapies in recurrent depression protocol (■ medication clinic and active imipramine; □ IPT-M and active imipramine; ● IPT-M alone; ○ IPT-M and placebo; ▲ medication clinic and placebo).

were in the range of 50–55% at the end of 2–3 years. These results suggest that the full-dose maintenance has a greater prophylactic effect than traditional reduced-dose maintenance strategies. Finally, it should be noted that patients receiving IPT-M alone or with placebo had a median survival time which was significantly greater than that of patients receiving medication clinic and placebo ($P = 0.04$). Thus, monthly IPT-M had some prophylactic value, but it did not approach the efficacy of full-dose medication. As Cuze & Freedman (1991) commented in their annual review of new developments in psychiatry for the *Journal of the American Medical Association*,

"These findings will require the reeducation of physicians and patients to the value of high-dose pharmacotherapy, and the need to seriously confront the risks of recurrence. Unipolar depression should be viewed as a chronic, disabling condition that follows a recurrent and episodic course for the majority of affected individuals and – as for bipolar disorders – sustained maintenance therapy is warranted. For this, IPT can be used alone, but clearly it is a far less potent factor than the high-dose pharmacotherapy."

The work yet to be done

These results do not mean, however, that the fight to 'conquer' serious mental disorders that Will Sargent began is over. Our knowledge of recurrent depressive disorder is far from complete; however, treatment studies such as the one just described can provide important leads to more fruitful investigation of the pathogenesis of the disorder. Furthermore, studies such as the one just described highlight the problems of our success.

The problems of our real success in the last decade may actually number more than four; however, attention should be drawn to four of our most prominent 'success problems'. First, we often achieve clear positive treatment effects within a few weeks. This may lead our colleagues to believe that they do not need to use the so-called 'high' or full dosages that we are recommending. However, we strongly advocate adequate dosage and regular monitoring of blood levels, if necessary to allay anxiety. Surprisingly large proportions of patients do not achieve adequate blood levels on even the upper end of the standard dose range. We urge clinicians to obtain blood levels and adjust the dose upward if indicated, before switching the patient to a second compound.

The second related problem of success is that many doctors stop medicating too early. Here I am referring not only to the failure to provide prophylaxis, but also to the failure to provide continuation treatment. Often the doctor 'colludes' with the patient and family in the illusion that the discontinuation of the medication means that that patient is well. Rather, we should seek to help patients and their families to redefine wellness in terms of the absence of symptoms and functional impairment. All too frequently, the 'collusion' leads to early discontinuation and increases the likelihood of relapse from 10 or 15% to 50%, ultimately making everybody unhappy.

A third problem is that we tend to forget that depression is a long-term problem, that our patients are likely to be with us for a long time, and that once they leave us they are likely to come back. And it is important that they return to us. It is important that we teach them early recognition of symptoms and encourage them to return at the earliest signs of change. This is critical if we are going to deal with the level of morbidity and potential mortality associated with this disorder.

Finally, a fourth problem of success, at least in the US, is insufficient attention in professional training. As much as we have learned about psychopharmacology, it is still clear that presently we do not devote enough professional training to the disorders requiring long-term management, including depression.

Recurrent affective disorder is now clearly understood to be a lifelong medical disorder, much like hypertension or diabetes. The results of the Pittsburgh study described above, as well as a number of studies that are beginning to come out using some of the newer drugs (e.g. Montgomery *et al.*, 1988), indicate that the dose that gets the patient better will also keep the patient well. However, this knowledge is helpful only if the patient can be convinced to continue to take the medication. We therefore believe more

strongly than ever that the art of developing and maintaining an alliance with patients and their families is absolutely central to our long-term approach to treatment of these disorders. We purposely do not use the word 'compliance' because we believe that the long-term treatment approach will be more successful if we work to establish alliances rather than to ensure unquestioning compliance.



The possible road to pathogenesis of the disorder

In the final section of this report, I should like to turn to an attempt to understand more about the disorder itself, using what we have learned from treatment to begin to integrate the diverse domains of the pathophysiology and perhaps, ultimately, the aetiology of depressive illness.

Our research group has been very interested in the application of biological measures to psychiatric disorders. In many ways the enthusiasm for such measures is derived from the era of Will Sargent's Watson-Smith Lecture. Today our enthusiasm may be somewhat tempered by the fact that it has not been simple to find incontrovertible biological markers. But this is perhaps because the early solutions were too simplistic, often ignoring the longitudinal aspects of these disorders. In general, we have thought about biological measures in two ways: as correlates of the disorder that are persistent, which we often refer to as 'traits', and as correlates of the disorder which are present only during the acute episode. Assuming that strategy, we hoped that biological correlates could be used to help us to understand the pathophysiology of the disorder and, perhaps, fulfil the expectation of a refinement in diagnostic criteria aided by biological measures.

Our strategy has been to think about biological correlates in a way that places them in the context of a model of the disorder. We have come to

distinguish between what will be referred to as Type 1 biological correlates, or persistent features of the disorder, and Type 2 correlates, or those associated with acute symptoms (Table 1) (Kupfer & Ehlers, 1989). We would argue that Type 1 correlates might be the very features that underlie the pathophysiology of the disorder. Furthermore, they may represent measures of vulnerability to the disorder, observable even in people who have never had an episode but are at risk, or they may represent biological scars, the residual effect of having had one or more episodes of depression.

When we refer to Type 2 correlates, we are identifying episodic features of the disorder. Such biological correlates may aid us in characterising subtypes, for example, delusional versus non-delusional, or endogenous versus non-endogenous. Biological correlates observable only during the acute episode may also help us to understand specific differences found in in-patients versus out-patients. Such differences cannot always be explained on the basis of how long the patient has been in the hospital, entrainment to ward routine, or the generalised stress of confinement, suggesting some more fundamental difference between in-patient and out-patient populations. Indeed, such differences may relate to the support systems available or the breakdown of those systems in the environment. Perhaps a more precise understanding of some of these episodic biological features will help us with many of these discriminations.

What current information is available that would support a Type 1 versus Type 2 discrimination? Such data are derived from a number of studies that have been conducted in sleep electrophysiology, as well as a host of studies that have sought to elucidate various neuroendocrine and neuropeptide pathways. For example, data suggest that slow-wave sleep reductions may be persistent in patients with recurrent affective disorders as compared with never-ill controls (Giles *et al.*, 1988). Recent support for this view comes from a study conducted at the Max Planck Institute (Krieg *et al.*, 1991), which pointed out that even high-risk probands, i.e. people who have never been depressed, show considerably less slow-wave sleep than age- and gender-matched controls. Furthermore, a series of reports from both the University of Texas and the University of Pittsburgh has indicated that unaffected family members – again, people who may be at high risk, but who have never experienced an episode – also have reduced slow-wave sleep. Our own studies (Kupfer & Ehlers, 1989) have suggested that patients with a history of recurrent depression who are studied while recovered, nevertheless still have slow-wave sleep that is significantly reduced as compared with that of age-matched controls.

Table 1
A biological model of recurrent depression

Biological correlates	Type 1 (persistent)	Type 2 (episodic)
Genetic/familial transmission	+++	+
Slow-wave sleep alterations	+++	+
REM sleep dysregulation	+	+++
Gender	++	+
Ageing	+++	+
Stress and severity related	+	+++
Neuropeptide factors	GRF (GH blunting)	CRF (HPA axis)

GRF, growth hormone releasing factor; CRF, corticotrophin releasing factor. + = minor relationship, ++ = moderate level of possible relationship, +++ = strong relationship.

Studies of growth hormone (GH) released by GHRH (growth-hormone-releasing factor), one of the major neuroendocrine pathways, have shown that recovered recurrent depressives continue to demonstrate reductions in growth hormone. Based on the Jarrett *et al* (1990) and Steiger *et al* (1989) studies, we can tentatively conclude that reduced growth-hormone secretion in depressed patients, observed at baseline, throughout the treatment of an acute episode, and into the drug-free remitted state, represents a trait or persistent marker in patients with recurrent depression. Studies of potential abnormalities of unstimulated diurnal GH secretion in depressed children and adolescents are inconclusive; however, blunted nocturnal GH secretion was found in suicidal depressed adolescents. This set of data is consistent with the numerous studies indicating blunting of GH in depressed patients following the administration of a variety of pharmacological probes.

As noted above, we view Type 2 abnormalities as representing 'episodic changes' associated with the presence of acute depressive symptoms. The considerable amount of data accumulated over the last 20 years on REM (rapid-eye-movement) sleep dysregulation in recurrent affective disorder may very well represent abnormalities which are episode-related rather than trait abnormalities. Several studies have suggested that very short onsets to REM sleep are associated with severe depression (Ansseau *et al*, 1984), but they are most strongly associated with delusional depression (Thase *et al*, 1986). Other investigations (Spiker *et al*, 1978) have suggested that the level of REM sleep dysregulation relates to the severity of the episode. Higher levels of dysregulation in in-patients versus out-patients have been noted (Kupfer *et al*, 1986). Several of the studies we have conducted in the last 5 years suggest that REM sleep dysregulation can be observed early in the episode of depression and may be even more prominent early in the episode of depression than later (Kupfer *et al*, 1988, 1991).

There is a controversy in the literature about whether REM sleep dysregulation normalises with recovery (Reynolds & Kupfer, 1987). While a number of studies suggest that REM sleep improves considerably once the episode is over, several other studies suggest that it may not. However, most data point to more prominent REM sleep dysregulation during the acute episode.

With respect to the hormonal pathways, a number of investigators both in the UK and the US have demonstrated abnormalities in the hypothalamic pituitary adrenal (HPA) axis during depressive episodes. Whether we examine the early dexamethasone suppression test (DST) data or the rather more sophisticated and more recent approaches to measuring the

HPA axis, or whether we discuss increased cortisol levels or the CRH (corticotrophin-releasing hormone) dexamethasone test, it is fairly well established that HPA axis abnormalities tend to normalise with clinical recovery. Von Bardeleben & Holsboer (1991) have shown in a group of 44 depressed patients that during the episode of depression, there is a considerable increase in the level of cortisol following escape from dexamethasone with the infusion of CRH, as compared with controls who have undergone the same procedure. Indeed, there are also some data to suggest that abnormalities in the HPA axis may be related to REM sleep dysregulation (Born *et al*, 1991). DeKloet (1991) has recently proposed that the negative feedback of corticosteroids upon limbic hypothalamic-pituitary activity is primarily mediated by:

- (a) glucocorticoid receptors in the nucleus paraventricularis and anterior pituitary corticotrophs
- (b) coordinate control of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the hippocampus.

Furthermore, it would appear that the effects of cortisol on REM sleep are GR mediated. The principal findings of von Bardeleben & Holsboer's group, documenting an increase of releasable cortisol after a combined dexamethasone-CRH administration, are consistent with the view that both corticosteroid receptor types, MRs and GRs, lose their capacity to respond adequately to glucocorticoid feedback signals in the course of depressive illness. This effect is apparently aggravated by increasing age.

Thus, we have the beginnings of a model which suggests a number of hypotheses requiring confirmation. Assuming that this model may be only one of perhaps several biological models for recurrent depression, we can none the less describe the following scheme.

Type 1 or persistent changes have much more to do with slow-wave sleep alterations than any other aspect of sleep and much more to do with GH and the GHRH and somatostatin pathways than with other neuroendocrine pathways. In normal subjects, GH responses to GHRH are usually augmented during slow-wave sleep as compared with those in waking state or during REM sleep, regardless of whether the time of sleep onset is normal or delayed (Holl *et al*, 1991). These results suggest that slow-wave sleep is associated with decreased hypothalamic somatostatin secretion, which facilitates the GH response to GHRH. Patients with depression showed alterations both in sleep pattern and GH release (Steiger *et al*, 1989). These persistent phenomena may very well be more genetically based than

environmental scars, and there is considerable evidence that both slow-wave sleep and growth hormone processes are much more affected by the ageing process than are other aspects of sleep or neuroendocrine pathways, and possibly more affected by gender.

We believe that *Type 2*, or *episodic changes* are strongly correlated with *REM sleep dysregulation*, less influenced by genetic, gender, or ageing factors, and more related to severity of illness and level of acute stress. Where does this speculation leave us in terms of a model of recurrent depression and how does this model relate to treatment? Type 2 alterations may convey information concerning appropriate strategies for acute treatment, while the Type 1 alterations may have more to do with what we should consider for long-term treatment strategies. This becomes apparent when we examine the biological response to treatment. For example, REM sleep is affected immediately by acute treatment manipulations (Kupfer *et al.*, 1987). One of the most striking things about all somatic treatments for depression is their tremendous impact on REM sleep in contrast to their relatively small impact on slow-wave sleep. It is true that slow-wave sleep is redistributed in response to acute somatic treatments; however, this redistribution may actually be secondary to changes in REM sleep. Finally, acute treatment clearly affects the HPA axis in a profound way; however, as noted above, there is almost no significant effect on pathways relating to growth hormone.

Moreover, I suggest that to predict or examine correlates for prophylactic strategies, we should focus on Type 1 alterations. If we study the sleep of depressed patients, we would conclude that they typically have an equal number of delta waves in the first non-rapid eye movement (NREM) period as compared with the second NREM period, or a 'delta sleep ratio' (Kupfer *et al.*, 1990) of 1 : 1. We were able to examine the sleep of the depressed patients that we followed in our long-term treatment trial. We were interested in whether we could predict their long-term outcome on the basis of their EEG sleep profile prior to their treatment. We found that patients with the lowest delta ratio had the shortest survival time before a new episode of depression. Patients who had a delta ratio which was closer to 2 : 1, approximately that of normal controls, had a much better chance of surviving the 3-year maintenance treatment trial without a new episode. These data suggest tentatively that we can build a framework on the Type 1 and Type 2 abnormalities observed and make predictions regarding both acute and long-term treatment.

Conclusions: the need for integrated longitudinal models

Despite the emphasis on biological factors, I wish to conclude by indicating that the pathway to understanding recurrent depression is perhaps not only a biological pathway. Until we have ample opportunity to develop and test integrated models that enable us to look at both psychosocial and biological determinants of a disorder, we may very well come up short in improving our understanding of depression. We have not devoted nearly enough attention to understanding affective and recurrent affective disorders that develop in childhood and adolescence, nor to the long-term prognosis of children so afflicted. We also need to emphasise recurrent disorder in the elderly much more, recognising that the patient who develops a first episode in the sixth decade of life may be at risk for another three decades. And, finally, although this report has been devoted solely to unipolar disorder, we will need to pay much more attention to bipolar disorder in order to understand the commonalities between recurrent unipolar and bipolar disorder. Not until we do that will we be in a position to understand fully the nature of recurrent affective disorder.

In conclusion, we should return to Will Sargent's Watson-Smith Lecture (1966). He concluded, and one could graft his conclusion onto the first William Sargent Lecture, that we *now* have modern empirical and physiological treatments to improve brain functioning. He said, "Only after this has been done can one set about treating and trying to help the *whole* man (or woman) with any hope of success. As the great Dr Samuel Johnson – himself a victim of recurrent melancholia – so aptly put it, 'Stay with me till I am well, and *then* you shall tell me how to cure myself' ". That is our charge in the treatment of recurrent depression – we need an integrated, humanistic, and scientific approach to the treatment of this serious disorder.

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